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SEMI-SOLID DISPERSION OF CARVEDILOL SOLID LIPID NANOPARTICLES FOR TOPICAL DELIVERY

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ABSTRACT

Nanoparticles have become one of the most active areas of research in the field of drug delivery due to their ability to deliver drugs to the right place at appropriate times and in the right dosage. Great progress has been made in the treatment of a variety of diseases by using drug delivery systems including solid lipid nanoparticles (SLN). The present study deals with the semi-solid dispersion of carvedilol solid lipid nanoparticles for topical delivery prepared by solvent injection method using stearic acid, PEG 6000, propylene glycol, chloroform, and distilled water. Four different formulations (F1 to F4) were prepared in different quantity of PEG 6000 and characterized by scanning electron microscopy, transmission electron microscopy, differential scanning calorimetry, particle size by zeta sizer, polydispersity index, encapsulation efficiency, and *in vitro* drug release study. Average size and polydispersity index of the best formulation, F3 was found to be 242 nm and 0.283 respectively. Encapsulation efficiency of F3 was found to be 87.9% with zero order release pattern.

KEYWORDS: Solid lipid nanoparticles, carvedilol, PEG.

INTRODUCTION

In last decade, significant attempt has been made to develop nanotechnology for drug delivery system, as it offers an appropriate means of delivering drugs whether small molecules or large molecules such as proteins, peptides or genes to cells and tissues and prevents them against enzymatic degradation.[1] Solid lipid nanoparticles (SLN) have emerged as a new drug delivery system with potential applications in pharmaceutical field, diagnosis, cosmetics, treatment and other allied sciences. In recent times, increasing attention has been focused on these SLN as colloidal drug carriers for incorporating lipophilic or hydrophilic drugs. Proteins, peptides and antigens intended for therapeutic purposes may be incorporated or adsorbed onto SLN, and further administered by parenteral and transdermal routes or other alternative routes such as nasal and pulmonary. SLN may be useful with conventional chemotherapy to overcome.[2]

Solid lipid nanoparticles are nanosize articles composed of mainly solid lipid and active drug. They were proposed as novel colloidal carrier in 1990s[3] and they are considered as a new generation of submicron sized emulsion or vesicles where the liquid lipid is replaced with solid lipid.[4] SLN combine the advantages of and avoiding some disadvantage of other colloidal vesicular systems.[5] SLN has advantage such as excellent physical stability, protection of labile drugs from degradation, controlled drug release at site, good tolerability and site specific targeting. They can carry both lipophilic and hydrophilic drugs. SLNs provide unique properties such as least size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals.[5]

SLNs are colloidal carriers developed as an alternative particulate carrier system to emulsions, liposomes and polymeric nanoparticles. SLNs combine the advantages and avoid the disadvantages of these colloidal carriers. Similar to emulsions and liposomes they are composed of physiologically well tolerated excipients and can be produced on large industrial scale by high pressure homogenization. Identical to polymeric nanoparticles their solid matrix protects incorporated active ingredients against chemical degradation and provides the highest flexibilities in the modulation of the drug release profiles.[6] Melike Üner et.al. reported solid lipid nanoparticles (SLN) to be an alternative system to emulsions, liposomes, microparticles and their polymeric counterparts. Altering surface characteristics by coating SLN with hydrophilic molecules like PEG improves plasma stability and biodistribution, and subsequent bioavailability of drugs entrapped.[7] Rahul Nair et.al. prepared solid lipid nanoparticles (SLN) of hydrophilic drug isoniazid (INH) by ethanol injection method using different combinations of tween 80 concentrations and varied sonication time which had significant effect on particle size, entrapment efficiency of SLN but not on

the drug release. The study suggested that SLN could be alternate method for prolonged drug release profiles and better therapeutic effect.[8] Thus, the present study was proposed to develop solid lipid dispersion of carvedilol nanoparticles and investigate for physicochemical characteristics, *in vitro* release and stability.

MATERIALS AND METHODS

Carvedilol was generously supplied as gift sample by Aurobindo Pharma Ltd, Hyderabad. Stearic acid, PEG 6000, propylene glycol and chloroform were procured from Loba Chemie Pvt. Ltd, Mumbai.

PRE- FORMULATION STUDIES

Fourier Transform Infra Red Spectroscopy (FTIR)

Compatibility of drug with the polymers was determined by FTIR Spectroscopy using Perkin Elmer RX1. The pellets were prepared by gently mixing of 1mg sample with 200mg potassium bromide at high compaction pressure. The scanning range was 450 to 4000 cm^{-1} and the revolution was 4 cm^{-1}. The pellets thus prepared were examined and the spectra of drug and the polymer in the formulations were compared with that of pure drug or polymer spectra.[9]

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetric curve of pure carvedilol, polymer and mixture of drug and polymer measurement were carried out by using Shimadzu (DSC-50 Kyoto, Japan) instrument equipped with a liquid nitrogen sub ambient accessory. 2-6mg samples were accurately weighed in aluminum pans hermetically sealed and heated at a rate of 10ºC per min in a 30 to 300º C temperature under nitrogen flow of 40 ml.[9]

PREPARATION OF STANDARD CURVE OF CARVEDILOL

Preparation of standard solution

100 mg of carvedilol was dissolved in 100 ml buffer pH 7.4. From this 5 ml of stock solution was diluted to 100 ml with pH 7.4 phosphate buffer thus giving a concentration of 50 µg/ml of the drug. Aliquots of standard drug solution ranging from 1ml to 9 ml were transferred to 10 ml volumetric flask and were diluted upto the mark with pH 7.4 buffer. Thus the final concentration ranges from 2- 20 µg/ml as per Beer's Lambert's Law. Absorbance of each solution was measured at 242 nm against buffer pH 7.4 as a blank and the concentration of drug Vs absorbance were plotted.[10]

PREPARATION OF CARVEDILOL LOADED SLNS

Solid lipid nanoparticles of carvedilol were prepared by solvent injection method given by Muller Goymann and Schubert,[11] with some modification. Stearic acid was melted and then carvedilol, propylene glycol and chloroform were mixed and dissolved with slight heating. Separately, PEG 6000 solution in an aqueous phase was prepared at the same temperature. Then, organic phase was quickly injected into aqueous phase at the same temperature with constant stirring using magnetic stirrer. Now, chloroform was evaporated with continuous stirring. SLN were formed and subjected to centrifugation at 9000 r/m for 50 min. This semisolid dispersion of SLN was used for the purpose of application on the skin for topical delivery of the drug.

Table 1. Formula of Carvedilol loaded SLNs

Ingredients	F1	F2	F3	F4
Carvedilol (mg)	6.25	6.25	6.25	6.25
Stearic acid (mg)	5	5	5	5
PEG-6000 (mg)	2	3	4	5
Propylene glycol (ml)	1	1	1	1
Chloroform (ml)	10	10	10	10
Distilled H_20	Upto 50ml	Upto 50ml	Upto 50ml	Upto 50ml

EVALUATION OF CARVEDILOL LOADED SOLID LIPID NANOPARTICLES

Fourier Transform Infra Red Spectroscopy (FTIR)

Drug and carrier interaction was studied by FT-IR Spectroscopy on pure drug and solid-lipid nanoparticles (Perkin Elmer RX1). The pellets were prepared by gently mixing of 1mg sample with 200mg potassium bromide at high compaction pressure. The scanning range was 450 to 4000 cm^{-1} and the revolution was 4 cm^{-1}. The pellets thus prepared were examined and the spectra of all the samples were compared.[9]

Scanning Electron Microscopy (SEM)

The Morphology of the SLNs was analyzed by scanning electron microscope (JEOL MODEL JSM 6400). The SLNs were mounted directly on the SEM stub, using double –sided, sticking tape and coated with platinum and scanned in a high vacuum chamber with a focused

electron beam. Secondary electrons, emitted from the samples were detected and the image formed.[12]

Transmission Electron Microscopy (TEM)

The morphological examination of carvedilol loaded SLNs was performed with TEM (model JEM-1230, Jeol, Tokyo, Japan).One drop of diluted sample was deposited on the surface of carbon coated copper grid and negatively stained with a drop of 2% (w/w) aqueous solution of phosphor tungestic acid for 30 Sec. Excess staining solution was wiped off by filter paper, leaving thin aqueous film on the surface. After being stained, samples were allowed to dry at room temperature for 10min for investigation.

Differential scanning calorimetry (DSC) analysis

DSC analysis was performed using Shimadzu Differential Scanning Calorimeter (DSC-50, Kyoto, Japan). About 10mg sample was added in a 40µl aluminium pan which was sealed and heated in the range of 30-300°C at a heating rate of 10°C /min. An empty aluminium pan was used as reference standard. Analysis was carried out under nitrogen purge.

Surface Characteristics by Zeta Potential

The Zeta potential of SLNs was measured on a zeta potential analyzer (Zetasizer 3000 HS Malvern instrument U.K). The samples were diluted with pH 7.4 and placed in eletrophoretic cell and measured in the automatic mode.[13]

Particle Size and Poly dispersity Index (PDI)

The particle size of SLNs was measured with a Malvern zeta sizer (Zetasizer 3000 HS Malvern instrument, U.K).The particle size distribution is reported as poly dispersity index. The sample were placed in the analyzer chamber and readings were performed at 25°c with a detected angle of 90°. [14]

Encapsulation efficiency and Loading capacity

The Encapsulation efficiency and loading capacity of the SLNs were determined by the separation of SLNs from the aqueous medium containing non associated carvedilol by cold centrifugation at 12000 RPM for 30 minutes. The amount of free carvedilol in the supernatant was measured by UV method at 242nm. [15] The carvedilol encapsulation efficiency (EE) and loading capacity (LC) of the SLNs were calculated as follows

$$Encapsulation\ efficiency = \frac{Total\ amount\ of\ carvedilol - Free\ carvedilol}{Total\ amount\ of\ carvedilol} \times 100$$

$$Loading\ capacity = \frac{Total\ amount\ of\ carvedilol - Free\ carvedilol}{Weight\ of\ nanoparticles} \times 100$$

***In vitro* diffusion studies**

The studies were performed on carvedilol and carvedilol SLNs in Phosphate buffer pH-7.4. Samples equivalent to 100mg of carvedilol were redispersed in 10ml pH-7.4 buffer solution and placed in a dialysis membrane bag with a molecular cut-off of (MWCO 12,000-15,000Da, Himedia, India) which acts as a donor compartment, tied and placed into 10 ml pH-7.4 buffer solution in a beaker which acts as a receptor compartment .The entire system was kept at 37ºC±0.1°C with continuous magnetic stirring at a rotation speed of 50 rpm. At appropriate time intervals (0min-14 hr) 1 ml of the release medium was removed through 0.1µm membrane filter immediately and 1 ml fresh pH-7.4 buffer solution was added in to the system. The amount of carvedilol in the release medium was evaluated by UV spectrophotometer at 242nm and the percentage release of carvedilol recorded. [16]

Stability Studies

The effect of temperature and humidity on the carvedilol SLNs was evaluated for 3 months under different storage conditions. The SLNs prepared were filled into an amber glass bottle and flushed with nitrogen gas prior to air-tight closure with a plastic cap. SLNs were then stored at freeze temperature (5°C±3°C), room temperature (25°C±2°C/60%±5%RH), and 40°C±2°C/75%±RH (as per ICH guidelines). The SLNs were evaluated for particle size, zeta potential value and PDI on 30th, 60th, 90th days. The percentage of drug release was assessed by UV analysis at 242nm after suitable dilution. [17]

RESULTS AND DISCUSSION

Standard curve of Carvedilol

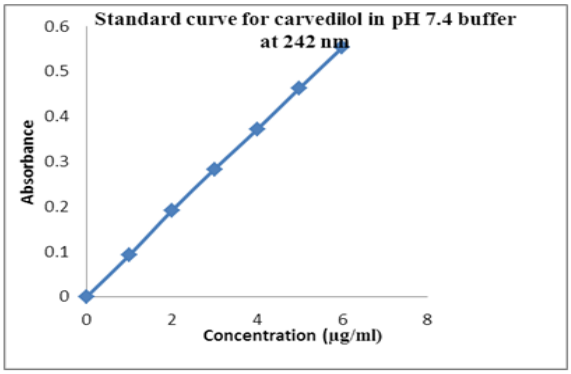

Fig. 1. Standard curve of Carvedilol in pH 7.4 buffer

COMPATIBILITY STUDY

Fourier transform- infrared

The Fourier transform-infrared (FTIR) spectra of pure drug, lipid, its physical mixture, and SLN formulation were obtained by using FTIR. It shows the characteristic peaks at 1606.76(C=O (stretching), 1454.38(C-O stretching), 3344.68(NH stretching), 3344.68(OH stretching), 960.58-424.35 Aromatic groups. All these peaks were present both in the physical mixture (drug and lipid) and drug loaded SLN, and there is no absence of any functional peaks in all the spectra. Thus, it reveals that there is no significant physicochemical interaction between drug and lipid in the formulation.

Fig. 2 shows the typical FTIR spectrum pattern of the solid lipid nano carvedilol in the range of 400 to 4,000 cm^{-1}. The IR spectrum of pure carvedilol showed the peak at 3,344.88 cm^{-1}, which corresponds to N-H

stretching. The hetero-aromatic structure shows the presence of the C-H stretching vibrations in the region 2995.87 cm^{-1} (C-H, Sp2) and at 2923.56 cm^{-1} which is the characteristic region for the ready identification of the C-H stretching vibrations. The bands corresponding to the in-plane C-H deformations are observed in the regions 1,000 to 1,300 cm^{-1}. The bands are sharp but of weak to minimum intensity. The medium and strong intensity bands are in the regions 1,099.72, 1,119.95, 1,156.24, and 1,177.15 cm^{-1} in the FT-IR spectrum. A medium experimental peak around 1252 to 1,402 cm^{-1} in the FT-IR was assigned to the C-C stretching vibrations. The bands in the regions 1,502 to 1,607 cm^{-1} observed in both FT-IR were assigned to the C = C stretching vibrations. In the present case, the bands observed at 849.50 and 783.90 cm^{-1} in the FT-IR are assigned to the ring breathing mode. The C-N stretching vibrations are seen in the regions 1,347.95 to 1,285.41 cm^{-1}. Thus, it is evident that the structure of the drug has no major change in the solid-lipid nano particles.

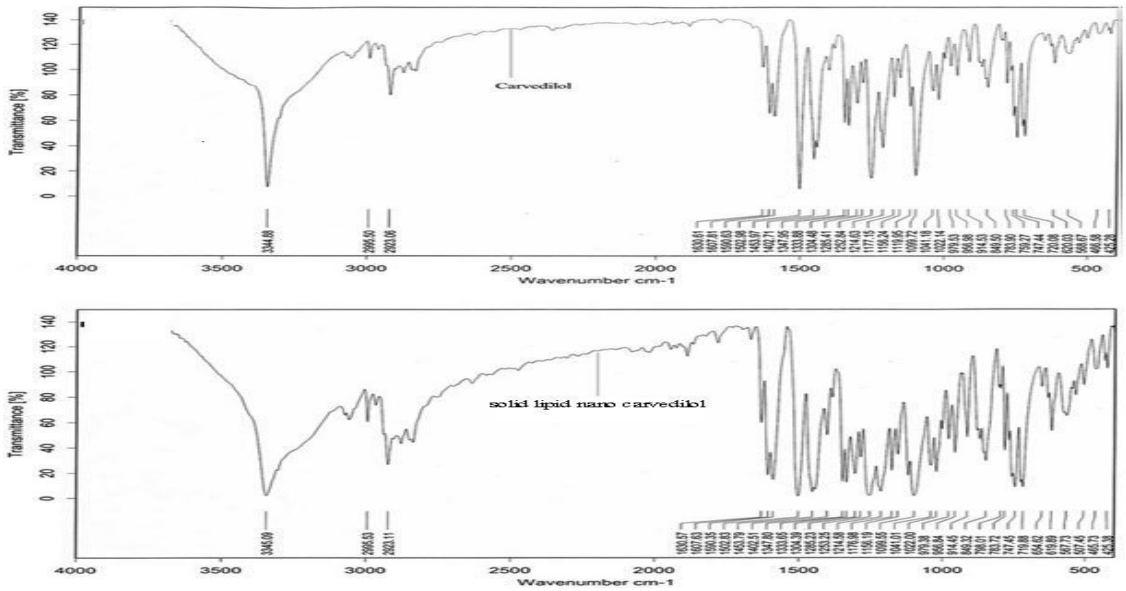

Fig. 2. FT-IR spectra of pure carvedilol and carvedilol SLNs

Differential scanning calorimetry (DSC)

The thermal behaviour of carvedilol and its solid lipid nanoparticles were studied using DSC to observe the effect of lipids on the carvedilol. The DSC thermograms of pure drug, lipid, physical mixture, and SLN formulation are shown in Fig.3. The differential scanning calorimetry (DSC) curve of carvedilol showed a sharp endothermic peak (Tpeak = 115°C) corresponding to its melting point, indicating its crystalline nature (Fig.3A). In DSC studies, the characteristic endothermic peaks, corresponding to the melting point of the drug were shifted toward higher temperature. This could be attributed to the bigger particle sizes and uniform distribution of drugs (Fig.3B). It is found that the melting temperature of carvedilol SLNs decreases with decreasing their particle size. The melting temperature increases as its size increases. In other words, their melting temperature is lower than the corresponding bulk materials.

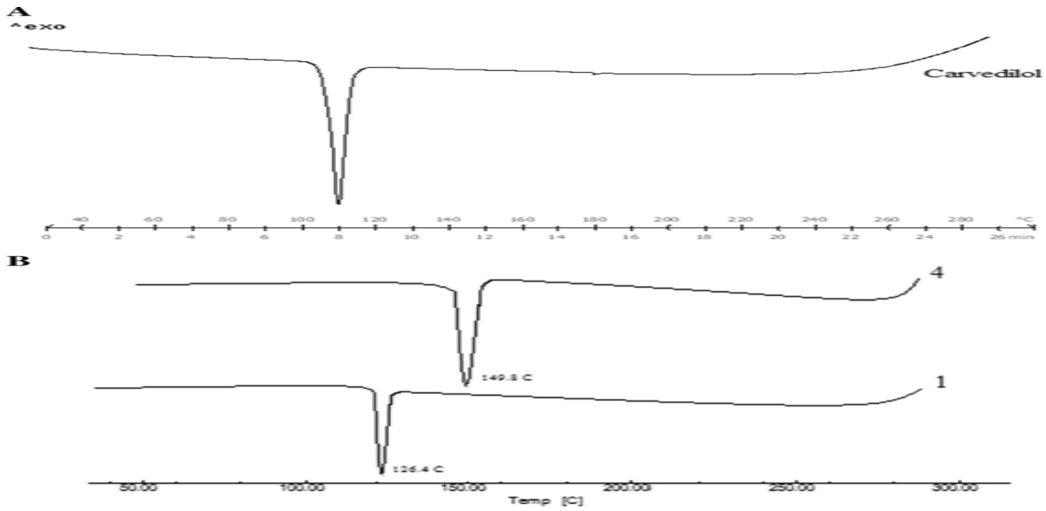

Fig. 3. DSC spectra of (A) carvedilol and (B) carvedilol SLNs

PHYSICO-CHEMICAL CHARACTERISTICS OF NANO PARTICLES

Surface morphology

Surface morphology of SLNs is shown in Fig. 4.It was found that the SLNs are spherical in shape with smooth surface, solid and dense with no aggregation.

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) studies were carried out for the formulations. The pictures reveal that the carvedilol SLNs were smooth and spherical. SLNs were of spherical shape with a regular surface profile. No indentations were observed on their surface (Fig. 4).

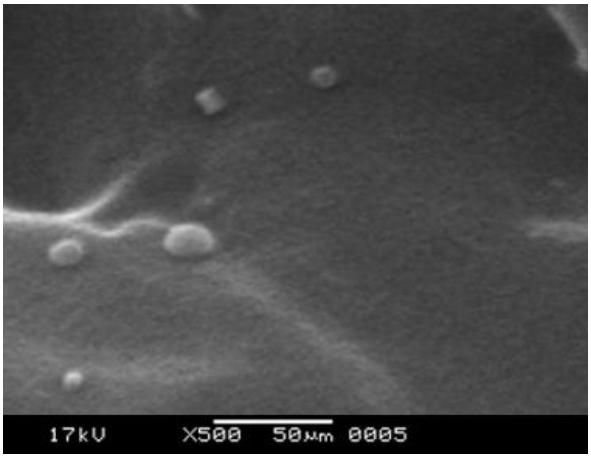

Fig. 4. SEM image of formulation F3

Transmission Electron Microscopy (TEM)

The results of TEM imaging of SLN formulations are shown in Fig. 5 which indicates that the particles had nanometer-size spherical shapes and no drug crystal was visible. The figures illustrate the presence of a very thin layer surrounding the particles which postulate a drug-enriched core model.

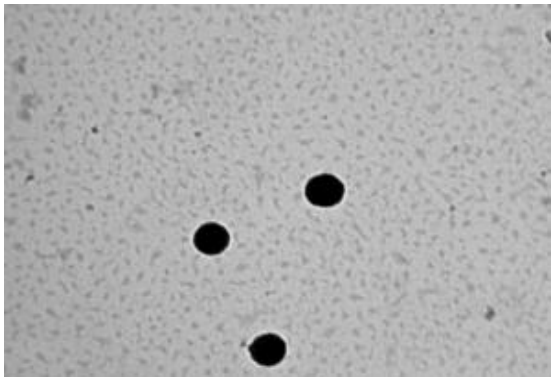

Fig. 5. TEM image of formulation F3

Particle size

In all formulations, the particle size ranged from 108.8nm to 358.2nm (Table 2).The results clearly show that there was a gradual decrease in particle size with an increase in surfactant concentration from 2, 3, 4, and 5 gm. This decrease in size at high surfactant concentrations might be due to effective reduction in interfacial tension between the aqueous and lipid phases leading to the formation of emulsion droplets of smaller size.

Zeta potential

Zeta potential of the SLNs was measured by Malvern zetasizer. The Zeta potential values of SLN which ranged from -35.3 ± 0.6 to -36.7± 0.8 (Table 2) were sufficient to keep the particles stable. The measurement of the zeta potential allows predictions about the storage stability of colloidal dispersion. In general, particle aggregation is less likely to occur for charged particles (high zeta potential) due to electric repulsion. The mean zeta potential was -35.325mv (n=4). Therefore, this method had gained a relatively good stability and dispersion quality. As depicted from the table, all formulations were negatively charged, indicating a relatively good stability and dispersion quality.

Poly dispersity index

The PDI of F1, F2, F3 and F4 are shown in Table 2. The mean poly dispersity index values for carvedilol SLNs varied in the range of 0.210 to 0.445(< 0.5) that indicates homogenous dispersion of drug in the formulation.

Table 2. Particle size, Zeta potential, PDI of carvedilol SLNs

Formulation Code	Particle size (nm)	Zeta potential (mV)	PDI
F1	108.8 ± 0.20	−36.7 ± 0.8	0.210 ± 0.22
F2	101.7 ± 1.30	−31.3 ± 0.8	0.201 ± 0.14
F3	102.7 ± 1.75	−35.3 ± 0.6	0.287 ± 0.24
F4	358.2 ± 2.05	−38 ± 1.0	0.445 ± 0.52

Encapsulation efficiency and loading capacity of the SLNs

Among the SLN formulations highest entrapment efficiency (88.7 ± 6.08%) was observed with formulation F2, whereas formulation F3 showed lowest entrapment efficiency (84.3 ± 5.61%) as shown in Table 3. As the lipid concentration is decreased there is a decline in entrapment efficiency of the SLN formulations.

Table 3. Encapsulation Efficiency and Loading Capacity of SLNs

Formulation code	Encapsulation efficiency (%)	Loading capacity (%)
F1	84.9 ± 4.49	85.8 ± 2.41
F2	88.7 ± 6.08	89.1 ± 4.48
F3	84.3 ± 5.61	87.9 ± 3.44
F4	85.2 ± 5.43	86.6 ± 7.11

***In vitro* diffusion study**

In order to evaluate the controlled release potential of the investigated formulations, the release of carvedilol from the lipid particles was investigated over 14h. Cumulative percent of drug release from the formulations F1 to F4 were found to be 94.29±0.52%, 98.2±0.40%, 99.1±0.42% and 94.61±0.15%. *In vitro* drug release performance of these formulations revealed that the release was governed by the concentration of PEG 6000.The results of the diffusion study of four formulations are shown in Fig. 6.

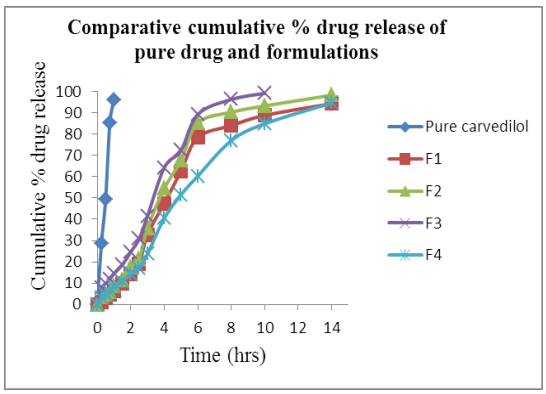

Fig. 6. Comparative diffusion profile of carvedilol solid lipid nanoparticles

STABILITY STUDY

All the formulations were stored in amber colored bottles at different temperature and relative humidity conditions. The effect of duration of storage and storage condition on entrapment efficiency of carvedilol SLNs is presented in Table 4. As the duration of storage increased the entrapment efficiency was found to be decreased. The good stability might derive from the slow transition of lipid in nano formulations and the steric effect of PEG 6000. These results clearly suggest that an optimum PEG 6000 concentration is sufficient to cover the surface of nanoparticles effectively and prevent agglomeration during the homogenization process. Stability studies reveal the physical stability of these lipid particles after 90 days of storage at different temperatures and there was no significant change observed in the cumulative % drug release of the formulations.

Table 4. Effect of temperature and duration of storage on formulation F3

Temp	Duration (days)	Size (nm)	PDI	Zeta potential
Freeze temp **(5°C±3°C)**	30	105.1 ± 0.15	0.289 ± 0.46	−34.8 ± 0.1
	60	112.3 ± 1.01	0.297 ± 0.88	−31.8 ± 0.6
	90	124.1 ± 0.95	0.317 ± 0.01	−28.3 ± 0.4
Room temp **(25°C±2°C/60%±5%RH)**	30	107.1 ± 1.15	0.291 ± 0.11	−32.3 ± 0.3
	60	115.3 ± 0.28	0.301 ± 0.81	−29.5± 0.1
	90	128.4 ± 1.05	0.322 ± 0.24	−24.1 ± 0.2
Elevated temp **(40°C±2°C/75%±5%RH)**	30	110.4 ± 0.75	0.299 ± 0.14	−30.8 ± 0.4
	60	119.2 ± 1.45	0.307 ± 0.28	−26.1± 0.5
	90	131.5 ± 1.09	0.325 ± 0.01	−21.9 ± 0.1

Table 5. *In- vitro* release profile of formulation F3 at different storage conditions

Time (min)	Cumulative % drug Release at freeze temp (5°C±3°C)			Cumulative %drug Release at room temp (25°C±2°C/60%±5%RH)			Cumulative %drug Release at 40°C±2°C/75%±5%RH		
	30 days	60 days	90 days	30 days	60 days	90 Days	30 days	60 days	90 Days
0	0	0	0	0	0	0	0	0	0
0.25	7.78±0.05	7.70±0.07	7.74±0.02	7.73±0.06	7.72±0.05	7.70±0.10	7.75±0.09	7.73±0.05	7.71±0.10
0.5	9.82±0.07	9.90±0.17	9.89±0.05	9.80±0.07	9.82±0.09	9.79±0.11	9.80±0.05	9.82±0.07	9.87±0.02
0.75	11.8±0.09	11.7±0.10	11.5±0.15	11.7±0.12	11.5±0.05	11.9±0.09	11.8±0.07	11.8±0.09	11.8±0.09
1.0	14.5±0.08	14.3±0.18	14.7±0.07	14.5±0.11	14.7±0.08	14.6±0.10	14.3±0.08	14.5±0.12	14.7±0.06
1.5	18.7±0.10	18.6±0.17	18.4±0.15	18.3±0.13	18.7±0.11	18.4±0.09	18.5±0.10	18.7±0.15	18.4±0.09

2.0	24.7±0.12	24.6±0.10	24.5±0.13	24.4±0.12	24.5±0.17	24.7±0.09	24.3±0.12	24.7±0.17	24.5±0.15
2.5	30.82±0.19	30.85±0.17	30.80±0.15	30.79±0.17	30.82±0.11	30.81±0.12	30.80±0.11	30.87±0.14	30.82±0.16
3	41.52±0.22	41.55±0.19	41.49±0.20	41.50±0.21	41.52±0.25	41.54±0.22	41.51±0.27	41.52±0.22	41.49±0.20
4	64.21±0.25	64.20±0.22	64.19±0.23	64.27±0.25	64.25±0.23	64.23±0.22	64.21±0.26	64.20±0.19	64.19±0.25
5	72.31±0.29	72.30±0.27	72.29±0.25	72.18±0.25	72.20±0.29	72.25±0.23	72.31±0.29	72.25±0.22	72.27±0.24
6	89.2±0.38	89.5±0.35	89.7±0.32	89.3±0.35	89.7±0.32	89.2±0.38	89.6±0.40	89.2±0.48	89.6±0.39
8	96.2±0.41	96.3±0.45	96.4±0.43	96.2±0.45	96.5±0.47	96.2±0.43	96.3±0.41	96.2±0.45	96.7±0.39
10	99.1±0.42	99.2±0.40	99.4±0.44	99.1±0.45	99.1±0.43	99.2±0.40	99.3±0.42	99.5±0.40	99.2±0.41

Solvent injection method is a reliable, simple and reproducible method for preparing SLN. In the present study, stearic acid was used as solid lipid and poly ethylene glycol 6000 as surfactant. In order to optimize the formulation, four different amounts of PEG 6000 were used with fixed amount of drug and lipid. All the formulations were analyzed in sequence to determine their particle size distribution and zeta potential values. Increase in the concentration of surfactant in SLN formulations could reduce the interfacial tension between lipid matrix and dispersion medium (aqueous phase) consequently favor the formation of SLN with smaller particle size. The results clearly suggest that an optimum concentration of polymer was sufficient to cover the surface of solid-lipid nanoparticles effectively and prevent agglomeration during the homogenization process. High concentration of surfactant was avoided to prevent decrease in the entrapment efficiency and also toxic effects associated with surfactant.

Zeta potential is a key factor to evaluate the stability of colloidal dispersion. It was currently admitted that zeta potentials above 30mV were required for full electrostatic stabilization. However, many experiments demonstrated that not only electrostatic repulsion dominated the stability of SLNs; the use of steric stabilizer also favored the formation of stable nanoparticle dispersion. It was noticeable that as the amount of surfactant increased in the formulation, the zeta potential became more negative.

Drug expulsion in SLN can occur when the lipid matrix transforms from high energy modifications, characterized by the presence of many imperfections, to the β-modification forming a perfect crystal with no room for guest molecules. The results indicate that as the lipid concentration is decreased there is a decline in entrapment efficiency of the SLN formulations.

It was evident from TEM images that SLNs were almost spherical with smooth morphology, appeared as black dots, well dispersed and separated on the surface. This description agrees with a previous observation that the use of stearic acid in combination with PEG 6000 favors the formation of ideally spherical lipid nanoparticles.

The amount and type of lipid and emulsifier affects the particle size, drug loading capacity and the stability of the formulation. The amount of lipid ought to optimum to encapsulate maximum amount of the drug and also should turn out minimum size lipid particles with narrow size distribution. The quantity of emulsifier should be optimum to cover the surface of the nanoparticles effectively and prevent agglomeration during the homogenization process, consequently favour the formation of SLN with smaller particle size and also be a factor to prevent decrease in the entrapment efficiency. Decrease in surfactant concentration results in decrease of particle size and have an influence on the drug release behavior form the SLN formulations but did not show any significant effect on % entrapment efficiency and stability of the formulations.

Cumulative percent of drug release from the formulations imply that the release behavior was governed by the concentration of the surfactant as well as the lipid used. The quantity of PEG 6000 should be optimum to cover the surface of the solid-lipid nanoparticles effectively and prevent agglomeration during the homogenization process, consequently favour the formation of SLN with smaller particle size and also be a factor to prevent decrease in the entrapment efficiency.

The obtained results show that the lipid material and surfactant concentration were the critical formulation variables and homogenization time was the important process aspect to prepare preferred SLN dispersions of carvedilol. The stability studies indicate that the carvedilol SLN formulations had good stability which might have derived from the slow transition of lipid in nano formulations and the steric effect of PEG 6000. These results clearly suggest that an optimum PEG 6000 concentration is sufficient to cover the surface of nanoparticles effectively and prevent agglomeration during the homogenization process.

CONCLUSION

The results of the present study indicate that solvent injection method is suitable to produce SLN of desirable size ranges. Drugs like carvedilol can be successfully loaded with lipids like stearic acid and surfactants like PEG 6000. The entrapment efficiency and the drug release profile depend on the concentration of the surfactant mixture employed. The drug release rate is controlled and based on the other properties of the SLN formulations. This system is most suitable for improving oral bioavailability of carvedilol. Stability studies reveal that after 90 days of storage at different temperatures the mean diameters of SLNs remain practically the same, which emphasize the physical stability of these lipid particles. These data collectively support that SLNs are

the promising delivery systems for drugs such as carvedilol.

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